REMARKS

Amendments to the specification

Applicants thank the Examiner for pointing out the typographical errors in the specification; these errors have been corrected in the instant amendment. Specifically, the error in the numbering of the paragraphs, beginning with the paragraph after paragraph [0028] on page 7, has been corrected. By this amendment, paragraph [0020] on page 7 through paragraph [0100] on page 24 have been renumbered as paragraphs [0029] through paragraph [0116], respectively.

In addition, the line immediately preceding renumbered paragraph [0037] (formerly paragraph [0028] on page 9 of the application as filed), has been renumbered as "iii. Amine agents". This is consistent with the previous subject headings (i.e., "i. Selective cyclooxygenase-2 inhibitory drug" and "ii. Sulphite compound"). Likewise, the line immediately preceding renumbered paragraph [0039] (formerly paragraph [0030] on page 10 of the application as filed) has been renumbered as "iv. Other excipients".

The typographical error in paragraph [0102] (formerly paragraph [0093] on page 20 of the application as filed), in which the reference to F1 should have been to F2, and the reference to F2 should have been to F1, has been corrected.

The dependent claims have been amended to replace "Claim" with "claim" as requested.

No new matter has been added by these amendments.

Status of the claims

Claims 1-31 are currently pending. Claims 7, 8, 11, and 17 stand withdrawn from consideration as being directed to non-elected subject matter.

Claims 1-6, 9, 10, 12-16, 18-20, and 25-31 stand rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement and as lacking enablement in the specification. Claims 1-6, 9, 10, 12-16, and 18-31 stand rejected under §112, second paragraph as being indefinite. Claims 1-6, 9, 10, 12-16, 18-20, and 25-29 stand rejected under §103(a) as being unpatentable over Black et al., U.S. Patent No. 5,733,909 ("Black") in view of Sakuma et al., European Patent No. 0 695 544 ("Sakuma"). Claims 21-24, 30, and 31 stand rejected under §103(a) as being unpatentable over Black in view of Sakuma and further in view of Tanida et al., U.S. Patent No. 6,214,378 ("Tanida"). Claims 1, 2, 10, 21-23, 28, 29, and 31 stand provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 19, 20, 23, and 26-31 of copending Application No. 10/633,102 (Attorney Ref. No. PC27433).

In order to focus the claims on the subject matter of greatest interest, claim 1 has been amended to specify that the fill material comprises celecoxib and sodium metabisulfite; claims 3, 13, and 30 have been amended to replace "Claim" with "claim" and to place the claim in better form (antecedent basis); claims 4, 6, 10, 12, 14-17, 19, 20, and 24-27 have been amended to replace "Claim" with "claim;" claim 5 has been amended consistent with the description found in original paragraph [0032] (now paragraph [0041]); the

reference to compounds in the plural has been removed; claim 9 has been amended consistent with the description found in original paragraph [0036] (now paragraph [0045]); the reference to compounds in the plural has been removed; and claim 18 has been amended to refer to propylene glycol in the singular. Support for these amendments may be found, for example, in original claims 2 and 23 and in the specification at paragraphs [0020] and [0027]. No new matter has been added by these amendments. Applicants reserve the right to pursue any cancelled subject matter in one or more continuation applications.

35 U.S.C. §112, first paragraph

Reconsideration is respectfully requested of the rejection of claims 1-6, 9, 10, 12-16, 18-20, and 25-31 under §112, first paragraph as failing to comply with the written description requirement and as lacking enablement in the specification.

The Office asserts that the specification does not adequately describe all possible dosage forms comprising (1) any selective cyclooxygenase-2 inhibitory drug of low water solubility and/or (2) any pharmaceutically acceptable sulfite compound. Furthermore, the Office asserts that the specification is not enabling of all possible selective COX-2 inhibitors of low water solubility and all possible pharmaceutically acceptable sulfite compounds. Without acquiescing as to these assertions, Applicants have amended claim 1 to specify that fill material comprises celecoxib and sodium metabisulfite. Thus, Applicants submit that all rejections of claims 1-6, 9, 10, 12-16, 18-20, and 25-31 under §112, first paragraph have been rendered moot.

35 U.S.C. §112, second paragraph

Reconsideration is respectfully requested of the rejection of claims 1-6, 9, 10, 12-16, and 18-31 under §112, second paragraph as being indefinite.

Applicants note that the phrase "low water solubility" is defined in the specification at paragraph [0027] ("having a room temperature solubility in water of not more than about 10 mg/ml and more preferably not more than about 1 mg/ml". Nevertheless, this phrase has been cancelled from claim 1, rendering moot the rejection of this claim.

Claim 5 has been amended consistent with the description found in original paragraph [0032] (now paragraph [0041]); the reference to compounds in the plural has been removed, rendering moot the rejection of this claim.

Claim 9 has been amended consistent with the description found in original paragraph [0036] (now paragraph [0045]); the reference to compounds in the plural has been removed, rendering moot the rejection of this claim.

Claim 18 has been amended to refer to propylene glycol in the singular, and thus this basis for the rejection of claim 18 has been rendered moot. Claim 18 does refer to polyethylene glycols. Such compounds are polymers, and as such can exist in forms having different molecular weights. See, e.g., *The Merck Index*, 13th Ed. (2001), pages 1358-59 (copy enclosed). Thus, Applicants submit that it is appropriate to refer to these solvents in plural form, and request reconsideration of the rejection of claim 18.

Claims 22, 28, 29, and 31 have been cancelled, rendering moot their rejection.

35 U.S.C. §103(a)

Reconsideration is respectfully requested of the rejection of claims 1-6, 9, 10, 12-16, 18-20, and 25-29 under §103(a) as being unpatentable over Black in view of Sakuma. Claims 2, 28, and 29 have been cancelled, rendering moot their rejection.

As amended, claim 1 is directed to a pharmaceutical dosage form comprising a fill material sealed in capsule shells wherein the fill material comprises (a) celecoxib and (b) at least one pharmaceutically acceptable sulfite compound selected from sodium metabisulfite, sodium bisulfite, and sodium thiosulfate, wherein the capsule shells comprise gelatin, and wherein the at least one pharmaceutically acceptable sulfite compound is present in a total sulfite amount sufficient to inhibit gelatin cross-linking and/or pellicle formation in the capsule shells upon storage of the dosage form.

A *prima facie* showing of obviousness requires, inter alia, that the cited references describe or suggest every limitation of the claimed invention. See MPEP 2143. Neither Black nor Sakuma describe a dosage form comprising a fill material sealed in capsule shells wherein the fill material comprises celecoxib, as required by claim 1. Thus, the Office has not shown that claim 1 (and claims 3-6, 9, 10, 12-16, 18-20, and 25-27 which depend from claim 1) is obvious in view of these references.

Reconsideration is respectfully requested of the rejection of claims 21-24, 30, and 31 under §103(a) as being unpatentable over Black in view of Sakuma and further in view of Tanida. Claims 21-23 and 31 have been cancelled, rendering moot their rejection.

Tanida describes capsules for oral preparations useful for colon diseases. These capsules are able to disintegrate only upon arrival in the large intestine (i.e., not in the stomach). As such, these capsules are said to be useful for colon diseases. This delayed disintegration is described as being provided by a capsule base consisting of hydroxypropylmethylcellulose ("HPMC"), a mixture of polyethylene glycol with HPMC, gelatin or agar that is successively coated with a cationic copolymer and an anionic copolymer. Tanida describes dozens of pharmaceutically active substances that may be encapsulated in his capsules; an example of such a substance is celecoxib (see col. 3, line 41).

Claim 24, like claim 1, is directed to a pharmaceutical dosage form comprising a fill material sealed in capsule shells wherein the fill material comprises (a) celecoxib and (b) sodium metabisulfite. Claim 24 further limits claim 1 by specifying that the celecoxib is present in an amount of about 10 to about 400 mg.

Claim 30 also depends from claim 1, and further limits claim 1 by requiring that the sodium metabisulfite **is present** in a total sulfite amount of about 0.5% to about 5% on a dry weight basis; that the fill material further comprises HPMC and/or polyethylene glycol; that the **celecoxib** is present in an amount of about 10 to about 400 mg; and that the capsule shells are soft gelatin capsule shells.

Neither Black nor Sakuma nor Tanida describe a dosage form comprising a fill material sealed in capsule shells wherein the fill material comprises celecoxib and sodium metabisulfite, as required by claim 1 (and claims 24 and 30). Thus, the Office has not shown that claims 24 and 30 are obvious in view of these references.

Non-statutory obviousness-type double patenting

Reconsideration of the provisional rejection of claims 1, 2, 10, 21-23, 28, 29, and 31 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 19, 20, 23, and 26-31 of copending Application No. 10/633,102 (Attorney Ref. No. PC27433) is respectfully requested. According to PAIR, copending application '102 is abandoned. Thus, Applicants respectfully submit that the provisional double patenting rejection is moot.

Conclusion

For the foregoing reasons, the Applicants submit that the present invention is now in condition for allowance. Allowance of all pending claims is respectfully solicited.

Respectfully submitted,

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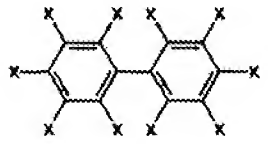
Accumulation of airborne PCBs in foliage: E. H. Buckley, *Science* **216**, 520 (1982). *Reviews:* H. L. Hubbard in *Kirk-Othmer Encyclopedia of Chemical Technology* vol. 5 (Interscience, New York, 2nd ed., 1964) pp 289-297; O. Hutzinger *et al., The Chemistry of PCBs* (CRC Press, Cleveland, Ohio, 1974) 269 pp; J. W. Lloyd *et al., J. Occup. Med.* **18**, 109-113 (1976). Reviews of environmental impact and toxicity: L. Fishbein, *Ann. Rev. Pharmacol.* **14**, 139-156 (1974); *National Conference on Polychlorinated Biphenyls*, Nov. 19-21, 1975 (EPA-560/6-75-004, 1976) 487 pp; R. D. Kimbrough, *Crit. Rev. Toxicol.* **2**, 445-498 (1974); S. H. Safe, *ibid.* **24**, 87-149 (1994). Reviews of carcinogenicity: *IARC Monographs* **18**, 43-103 (1978); E. M. Silberhorn *et al., Crit. Rev. Toxicol.* **20**, 439-496 (1990); of toxicology and mechanism of action: S. Safe, *ibid.* **13**, 319-395 (1984); of toxicology and human exposure: *Toxicological Profile for Polychlorinated Biphenyls* (PB93-182517, 1993) 23 p.



X = H or Cl

Aroclor 1242. Clear, mobile liquid; av. number Cl/molecule: 3.10. d_4^{25} 1.381, d_4^{55} 1.392. Distillation range 325-366°. Flash point (open cup) 348-356°F. n_D^{20} 1.627-1.629. Dielectric constant (1000 cycles) 5.6 (25°), 4.9 (100°).

Aroclor 1254. Light yellow, viscous liquid; av. number Cl/molecule: 4.96. d_4^{65} 1.495; d_4^{55} 1.505. Distillation range 365-390°. No open cup flash point to boiling. n_D^{20} 1.629-1.641. Dielectric constant (1000 cycles) 5.0 (25°), 4.3 (100°). LD_{50} orally in weanling rats: 1295 mg/kg (Kimbrough).

Aroclor 1260. Light yellow, soft, sticky resin; av. number Cl/molecule: 6.30. d_4^{65} 1.555; d_4^{55} 1.566. Distillation range 385-420. No open cup flash point to boiling. n_D^{20} 1.647-1.649. Dielectric constant (1000 cycles) 4.3 (25°); 3.7 (100°). LD_{50} orally in weanling rats: 1315 mg/kg (Kimbrough).

Caution: In Japan, 1968, oral intoxication to humans due to accidental contamination of rice bran oil with Kanechlor 400 led to an outbreak of what became known as "Yusho disease". Symptoms of oral intoxication in humans included nausea, lethargy, chloracne, brown pigmentation of skin and nails, subcutaneous edema of the face, distinctive hair follicles, excessive eye discharge, swelling of eyelids, visual disturbances, GI disturbances and jaundice. *See* M. Kuratsune *et al.*, (EPA-560/6-75-004, 1976) p 14. Potential symptoms of occupational overexposure are chloracne, dermal lesions; hepatic injury; decreased pulmonary function; decreased birth weight in offspring of exposed mothers; eye irritation (Safe, 1994). *See also Patty's Industrial Hygiene and Toxicology* vol. 2D, G. D. Clayton, F. E. Clayton, Eds. (John Wiley & Sons, Inc., New York, 4th ed., 1994) 2433-2504. These substances are reasonably anticipated to be human carcinogens: *Ninth Report on Carcinogens* (PB2000-107509, 2000) p III-186.

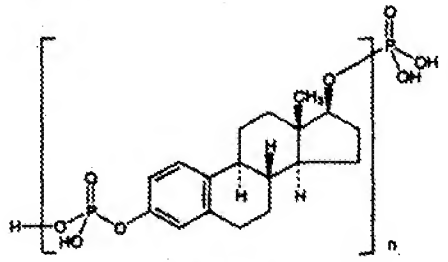
USE: In electrical capacitors, electrical transformers, gas-transmission turbines, vacuum pumps. Formerly used in U.S. as hydraulic fluids, plasticizers, adhesives, fire retardants, wax extenders, dedusting agents, pesticide extenders, inks, lubricants, cutting oils, in heat transfer systems, carbonless reproducing paper.

7648. Polydextrose. [68424-04-4] Litesse. Randomly bonded condensation polymer of dextrose with small amounts of bound sorbitol and citric acid. Functions to replace the bulk and mouthfeel of sugar and/or fat in reduced calorie foods. Prepn: H. H. Rennhard, US 3766165 (1973 to Pfizer). Improved process: D. B. Guzek *et al.*, EP 473333 (1992 to Pfizer); C.A. **116**, 237725s (1992). Reviews of physical properties and applications in foods: A. Torres, R. D. Thomas, *Food Technol.* **35**, 44-49 (1981); F. K. Moppett in *Food Sci. Technol.* **48**, entitled "Alternative Sweeteners", L. O. Nabors, R. C. Gelardi, Eds. (1991) pp 401-421.

White to light tan, amorphous powder, mp >130°. Bland, non-sweet taste. Hygroscopic. pH of 10% w/w aq soln: 2.5-3.5. Viscosity of 50% aq soln: 35 cps. Very sol in water (to ~80%). Partially sol in glycerin, propylene glycol. Insol in ethanol. Caloric utilization value in humans: 1 kcal/g.

USE: Bulking agent for reduced calorie foods.

7649. Polyestradiol Phosphate. [28014-46-2] Estradiol phosphate polymer; PEP; Estradurin. Polymeric ester of phosphoric acid and estradiol. Mol wt ~26,000. Prepn: Diczfalusy, *Endocrinology* **54**, 471 (1954); Fernö *et al., Acta Chem. Scand.* **12**, 1675 (1958); Diczfalusy *et al.*, US 2928849 (1960 to AB Leo). Clinical pharmacology: P. O. Gunnarsson, B. J. Norlén, *Prostate* **13**, 299 (1988). Clinical trial in prostatic carcinoma: J. Aro, *ibid.* **18**, 131 (1991).

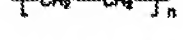


n is approx. 80

Solid, mp 195-202°. Very sol in aq pyridine; sol in aq alkali; very slightly sol in ethanol, ethanol + water (1:1), water, dioxane, acetone, chloroform. Intrinsic viscosity [η] in 0.25*M* NaCl soln at pH 7.5 ≈ 0.04.

THERAPEUTIC CAT: Antineoplastic (hormonal).

7650. Polyethylene. [9002-88-4] Ethene homopolymer; Agilene; Alathon; Alkathene; Courlene; Lupolen; Petilon; Polythene; Pylen; Reevon. Mol wt about 1500-100,000. C 85.7%, H 14.3%. Prepd by polymerization of liq ethylene at high temps and high or low pressure. *Reviews:* Aggarwal, Sweeting, *Chem. Rev.* **57**, 665-742 (1957); Raff, Allison, *Polyethylene*, vol. XI of High Polymers series (Interscience, New York, 1956); Faith *et al., Industrial Chemicals* (Wiley, New York, 3rd ed., 1965) pp 624-630.



Plastic solid of milky transparency. d_4^{20} 0.92. Tough and flexible at room temps, mp 85-110°. Breaks with cryst fracture at −50°. Good electrical insulator. Surface resistivity: 10^{14} ohms. Will burn, but hardly supports combustion. Stable to water, non-oxidizing acids and alkalies, alcohols, ethers, ketones, esters at ordinary temps. Attacked by oxidizing acids such as nitric acid and perchloric acid, free halogens, benzene, petr ether, gasoline and lubricating oils, aromatic and chlorinated hydrocarbons.

USE: Laboratory tubing; in making prostheses; electrical insulation; packaging materials; kitchenware; tank and pipe linings; paper coatings; textile stiffeners.

7651. Polyethylene Glycol. [25322-68-3] α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl); macrogol; PEG; Carbowax; Pluracol E; Poly-G; Polyglycol E. Liquid and solid polymers of the general formula $H(OCH_2CH_2)_nOH$, where *n* is greater than or equal to 4. In general, each PEG is followed by a number which corresponds to its average mol wt. Synthesis: Fordyce, Hibbert, *J. Am. Chem. Soc.* **61**, 1905, 1910 (1939). *Reviews: Glycols*, G. O. Curme, Jr., F. Johnston, Eds., A.C.S. Monograph Series no. 114 (Reinhold, New York, 1952) pp 176-202; Kastens in *High Polymers*, H. Mark *et al.*, Eds., vol. 13 entitled *Poly-*

ethers, part 1 (Interscience, New York, 1963) pp 169-189, 274-291; G. M. Powell, III in *Handbook of Water-Soluble Gums & Resins*, R. L. Davidson, Ed. (McGraw-Hill, New York, 1980) pp 18/1-18/31.

Clear, viscous liquids or white solids which dissolve in water forming transparent solns. Sol in many organic solvents. Readily sol in aromatic hydrocarbons. Only slightly sol in aliphatic hydrocarbons. Do not hydrolyze or deteriorate on storage, will not support mold growth. Solvent action on some plastics. Polyethylene glycols are compds of low toxicity: Smyth *et al., J. Am. Pharm. Assoc., Sci. Ed.* **39**, 349 (1950). Toxicity data (PEG 400): W. Bartsch *et al., Arzneimittel-Forsch.* **26**, 1581 (1976).

Polyethylene glycol 200. Average value of n is 4, mol wt range 190-210. Viscous, hygroscopic liq; slight characteristic odor; d_{25}^{25} 1.127. Viscosity (210°F): 4.3 centistokes. Supercools upon freezing.

Polyethylene glycol 400. Average value of n between 8.2 and 9.1, mol wt range 380-420. Viscous, slightly hygroscopic liq; slight characteristic odor; d_{25}^{25} 1.128, mp 4-8°. Viscosity (210°F): 7.3 centistokes. LD_{50} orally in rats: 30 ml/kg (Bartsch).

Polyethylene glycol 600. Average value of n between 12.5 and 13.9, mol wt range 570-630. Viscous, slightly hygroscopic liq; characteristic odor; d_{25}^{25} 1.128, mp 20-25°. Viscosity (210°F): 10.5 centistokes.

Polyethylene glycol 1500. Average value of n between 29 and 36, mol wt range 1300-1600. White, free-flowing powder; d_{25}^{25} 1.210, mp 44-48°. Viscosity (210°F): 25-32 centistokes.

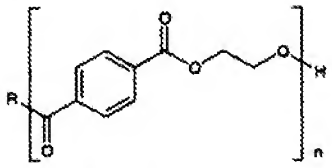
Polyethylene glycol 4000. Average value of n between 68 and 84, mol wt range 3000-3700. White, free-flowing powder or creamy-white flakes; d_{25}^{25} 1.212, mp 54-58°. Viscosity (210°F): 76-110 centistokes. LD_{50} orally in rats (divided doses): 59 g/kg (Smyth).

Polyethylene glycol 6000. Average value of n between 158 and 204, mol wt range 7000-9000. Powder or creamy-white flakes; d_{25}^{25} 1.21, mp 56-63°. Viscosity (210°F): 470-900 centistokes. LD_{50} orally in rats: >50 g/kg (Smyth).

USE: As water-soluble lubricants for rubber molds, textile fibers, and metal-forming operations. In food and food packaging. In hair prepns, in cosmetics in general. Pharmaceutic aid (ointment and suppository base). As a stationary phase in gas chromatography. Also in water paints, paper coatings, polishes and in the ceramics industry.

THERAP CAT (VET): Ointment base.

7652. Polyethylene Terephthalates. PET. Fiber forming polyesters prepd from terephthalic acid, *q.v.* or its esters and ethylene glycol: Whinfield, Dickson, US **2465319** (1949 to du Pont). Review of structures, definition of trade names: R. W. Moncrieff, *Man-Made Fibres* (John Wiley & Sons, New York, 4th ed., 1963) pp 361-389, 707-723.

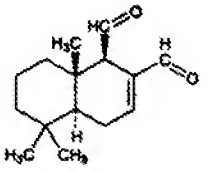


Dacron R = OH
Terylene R = OCH_3

R = OH, ***Dacron***, ***Amilar***, ***Fiber V***. Solid, dec at approx 250°. Sp gr 1.38. Sol in hot *m*-cresol, trifluoroacetic acid, *o*-chlorophenol, a mixture of 7 parts of trichlorophenol and 10 parts (by wt) of phenol, a mixture of 2 parts of tetrachloroethane and 3 parts (by wt) of phenol. Fiber has good resistance to weak acids even at boiling temp, to strong acids in the cold, to weak alkalies, to bleaches, to most alcohols, ketones, soaps, detergents, and dry cleaning agents. Fabric has good resistance to creasing, abrasion, heat aging, and sunlight when behind glass. When "heat-set", fabric will not shrink in either boiling water or boiling drycleaning solvent. Fabric burns, but local melting generally prevents spread of fire. Insects cannot thrive on the fiber, but some can cut through it. Molds, mildew, and fungi may grow on applied finishes, but do not attack fiber. R = OCH_3, ***Terylene***. For physical properties, *see* Dacron above. Other similar products: ***Diolen***, ***Enkalene***, ***Fortrel***, ***Tergal***, ***Terital***, ***Terlenka***, ***Trevira***, ***Mylar***.

USE: In fabric manufacture; as films; as base for magnetic coatings. Surgical aid (arterial grafts).

7653. Polygodial. [6754-20-7] (1*R*,4a*S*,8a*S*)-1,4,4a,5,6,-7,8,8a-Octahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxaldehyde; tadeonal. $C_{15}H_{22}O_2$; mol wt 234.33. C 76.88%, H 9.46%, O 13.66%. Widely distributed drimane sesquiterpene with insect antifeedant properties; naturally occurring as the (−)-form. Isoln from *Polygonum hydropiper* L., *Polygonaceae* (Australia) and structure: C. S. Barnes, J. W. Loder, *Aust. J. Chem.* **15**, 322 (1962); from the bark of *Warburgia stuhlmanni* Engl. or *W. ugandensis*, *Canellaceae* (E. Africa): I. Kubo *et al., Chem. Commun.* **1976**, 1013; from nudibranch *Dendrodoris limbata* (Mediterranean): G. Cimino *et al., Science* **219**, 1237 (1983); from nudibranchs *D. nigra*, *D. tuberculosa* (Hawaii) and *D. krebsii* (Mexico): R. K. Okuda *et al., J. Org. Chem.* **48**, 1866 (1983). Relationship between structure and antifeedant-activity: K. Nakanishi, I. Kubo, *Isr. J. Chem.* **16**, 28 (1977); M. D'Ischia *et al., Tetrahedron Letters* **1982**, 3295. Synthesis of racemate: T. Kato *et al., Tetrahedron Letters* **1971**, 1961; S. C. Howell *et al., Chem. Commun.* **1981**, 507. Synthesis of (−)-form: I. Razmilic *et al., Synth. Comm.* **17**, 95 (1987).



Colorless needles from petroleum (40-60°), mp 57° (Barnes, Loder). $[\alpha]_D^{24}$ −131° (c = 0.96 in ethanol). uv max (ethanol): 231, 295 nm (ε 11800, 76).

(±)-Form. mp 93-94° (Tanis, Nakanishi).

7654. Polylysine. [25104-18-1] L-Lysine, homopolymer. A lysine polypeptide or homopolymer, the chain length of which varies with the method of prepn. Prepn: Katchalski *et al., J. Am. Chem. Soc.* **69**, 2564 (1947); **70**, 2094 (1948); Fasman *et al., ibid.* **83**, 709 (1961); Sela *et al., Biopolymers* **1**, 517 (1963); Strojny, White, US **3215684** (1965 to Dow). For structure *see* Lysine.

L-Form hydriodide. Average dp (or n) = 32. Transparent, solid, film-like polymer. Readily sol in water; practically insol in the usual organic solvents. Transition of high-mol-wt poly-L-lysine (dp 1500) in aq soln from a helical to a randomly coiled conformation under the influence of decreasing pH or increasing temp: Applequist, Doty, *C.A.* **58**, 6925b (1963).

7655. Polymerized Pyridoxylated Hemoglobin. Poly SFH-P; PolyHeme. Acellular oxygen carrier consisting of pyridoxylated, stroma-free hemoglobin polymerized with glutaraldehyde. Average mol wt 150 kDa. Prepn and oxygen-carrying capacity: L. R. Sehgal *et al., Prog. Clin. Biol. Res.* **122**, 19 (1983); *eidem, Surgery* **95**, 433 (1984). Pharmacology: S. A. Gould *et al., Ann. Emerg. Med.* **15**, 1416 (1986). Clinical trial in acute blood loss: *idem et al., J. Am. Coll. Surg.* **187**, 113 (1998). Review of clinical development: S. A. Gould, G. S. Moss, *World J. Surg.* **20**, 1200-1207 (1996).

Prepd as solution containing 12-14 g hemoglobin/dl. Oxygen-carrying capacity: 16-19 vol%. Binding coefficient (ml O_2/g Hb): 1.30. Colloid osmotic pressure: 20-25 mm Hg.

THERAP CAT: Blood substitute.

7656. Polymyxin. [1406-11-7] Antibiotic complex produced by *Bacillus polymyxa*: Brownlee, Jones, *Biochem. J.* **43**, XXV (1948). Prepn: Ainsworth, Pope, US **2565057** (1951 to Burroughs Wellcome); Petty, US **2595605** (1952 to Am. Cy-